Organic & Biomolecular Chemistry

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Using singlet oxygen to synthesise the CDE-ring system of the pectenotoxins†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 537

Received 6th November 2012,
Accepted 22nd November 2012

DOI: 10.1039/c2ob27158c

www.rsc.org/obc

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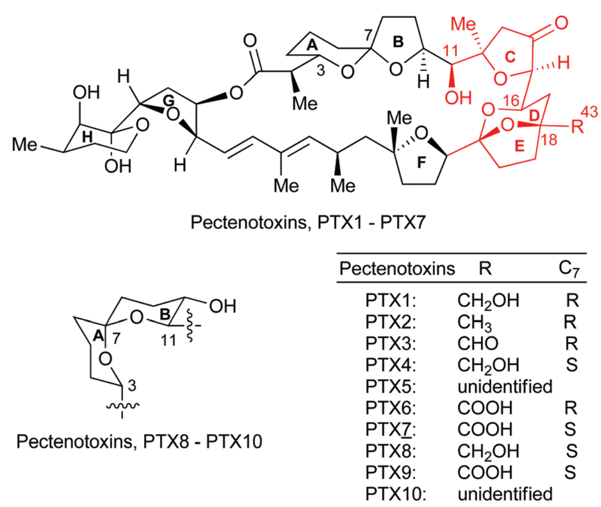
A non-classical route to the key CDE-ring fragment of the pectenotoxins has been developed which showcases a remarkable singlet oxygen-mediated cascade reaction sequence to install the complete DE ring system.

The pectenotoxin (PTX, Fig. 1) family of natural products has attracted a great deal of attention from different groups of researchers in recent years, not only because of their biological activity which has been shown to possess certain new and exciting features, but also by reason of the structural challenges to synthesis that they exhibit. Originally isolated[1a] from the host shellfish (a scallop named, *Patinopecten yessoensis*), the pectenotoxins are actually produced by dinoflagellates found worldwide in coastal waters.[1] However, the scarcity of samples available from natural sources has hindered the pursuit of further studies into the PTXs' potentially useful cytotoxicity[2] (achieved *via* a novel mode of F-actin disruption[2b]). Thus, finding effective new means to access these compounds synthetically in larger quantities would serve a very useful purpose.

In general, synthetic strategies towards polyoxygenated targets frequently rely heavily on cumbersome redox shuttling (manipulation and differentiation of the oxygen functionalities by repeated back and forth alterations to their oxidation states often using ungreen reagents) and on the use of an excessive number of unconstructive oxygen functionality protections and deprotections.[3] The primary focus of our research of late[4] has been to develop new singlet oxygen-based methods for the synthesis of just such polyoxygenated motifs, which, by virtue of the ability of singlet oxygen to orchestrate cascade reaction sequences and its inherent selectivity, help us to avoid many of these common pitfalls. Herein, we present one such effort



Pectenotoxins	R	C_7
PTX1:	CH_2OH	R
PTX2:	CH_3	R
PTX3:	CHO	R
PTX4:	CH_2OH	S
PTX5:	unidentified	
PTX6:	COOH	R
PTX7:	COOH	S
PTX8:	CH_2OH	S
PTX9:	COOH	S
PTX10:	unidentified	

Fig. 1 The pectenotoxin family of natural products.

in the form of a non-classical route affording the key CDE-ring[5] fragment of the PTXs. When combined with our earlier successful singlet oxygen-mediated one-pot "super-cascade" which synthesised the ABC-ring section,[6] this serves to illustrate the full synthetic potential of this powerful and green oxidant.[4a]

PTXs 4 and 8 are the only members of the family which have been successfully synthesised[7] in the laboratory; however, many efforts have been reported, which are directed towards synthesis of specific fragments of these molecules.[6,8] Our current CDE-ring work joins the recent elegant efforts of Pihko,[9] Brimble,[10] and Micalizio[11] who have published their own investigations (following on from earlier work undertaken by the Roush group[12]) directed towards PTX fragments including these particular rings. Furthermore, it should be noted that the groups of both Paquette[13] and Fujiwara[14] have completed PTX sections which include the necessary but, as yet, uncyclised backbone of the DE-bicycle section.

Our own synthetic blueprint (Scheme 1) was based on the idea that a simple furanyl butanone unit could be united

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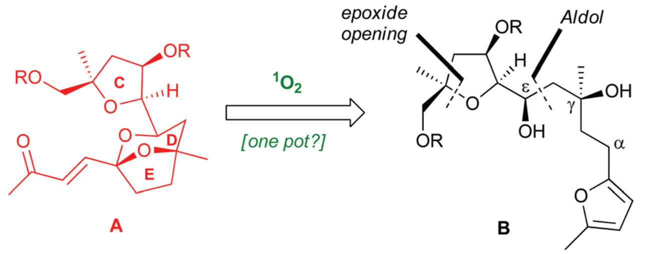
†Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data and copies of ^1H and ^{13}C NMR spectra for all new compounds, as well as copies of the NOE experiments. See DOI: 10.1039/c2ob27158c



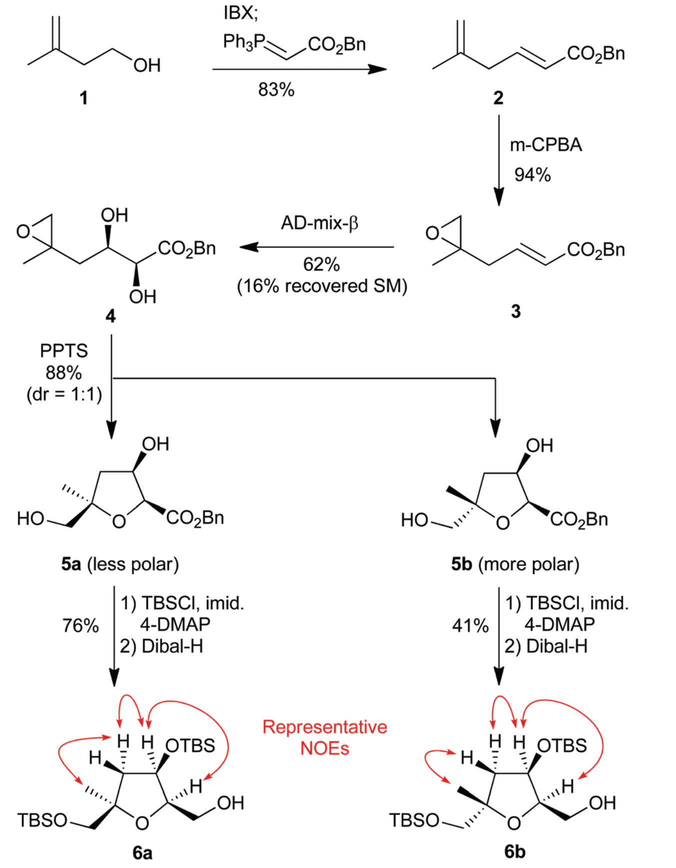
Scheme 1 Proposed synthetic plan.

readily with an intact pre-synthesised C-ring fragment (using an aldol condensation) and then methylated in such a way as to leave hydroxyl functionalities at the γ- and ε-positions of the alkyl side chain appended to the 2-position of the furan **B** (Scheme 1).

It was hoped that this newly acquired homochiral substrate would then succumb to an ambitious singlet oxygen-initiated reaction cascade sequence (in which these two pendant hydroxyl functionalities would participate) that would in a rapid and extremely efficient manner construct the requisite DE-ring motif, and thus, afford the completed CDE-ring section of the pectenotoxins (**A**, Scheme 1). We had previously investigated such a cascade for accessing simple 2,8-dioxabicyclo[3.2.1]octane model compounds and had recorded successes both in organic solvents and in water.[15]

To explore the practicality of this proposal we begun by developing a C-ring synthesis in which we chose to implement fairly obvious disconnections in the forward synthetic sense. Thus, it was anticipated that a 5-*exo*-epoxide opening (Scheme 1) of an appropriately substituted epoxide by a hydroxyl group would be the easiest means by which to construct the desired tetrahydrofuran ring, and before this cyclisation step, the requisite vicinal diol unit could be generated using a Sharpless asymmetric dihydroxylation reaction.

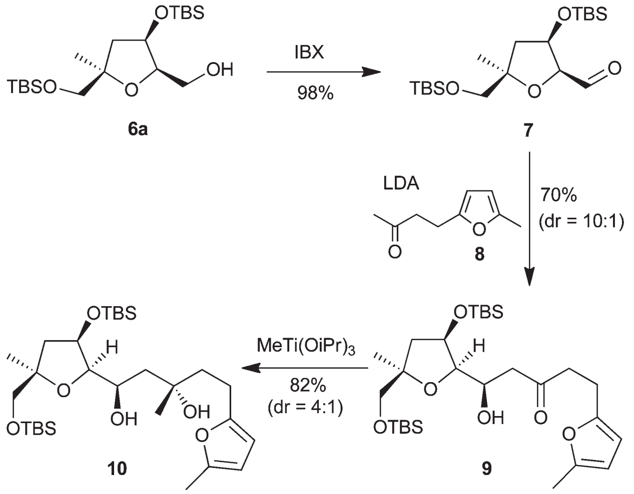
To this end, the commercially available and cheap homoallylic alcohol **1** was oxidised using IBX and a solution of the resultant volatile aldehyde (not isolated) was treated directly with the stabilised ylide Ph_3PCHCO_2Bn to afford diene **2** (*trans* : *cis* isomers = 9 : 1) in an overall yield for the two steps of 83% (Scheme 2). Chemoselective epoxidation of diene **2** with *m*-CPBA in buffered ($NaHCO_3$) DCM afforded epoxide **3** in 94% yield. AD-mix-β was then used to install the requisite vicinal diol unit at the site of the more electron deficient double bond (**3** → **4**, 62% with 16% recovered starting material). The benzoate ester had been chosen for inclusion in the substrate (from the earlier Wittig reaction) to improve the difficult isolation of the diol product from this aqueous dihydroxylation reaction; indeed, the analogous (to **4**) methyl ester had been synthesised, but could only be isolated in low yields, and, furthermore, its quantities were further depleted on purification and manipulation due to its polarity and poor solubility in organic solvents. Catalytic acid (PPTS, 10 mol%) was then used to effect the desired cyclisation reaction to afford



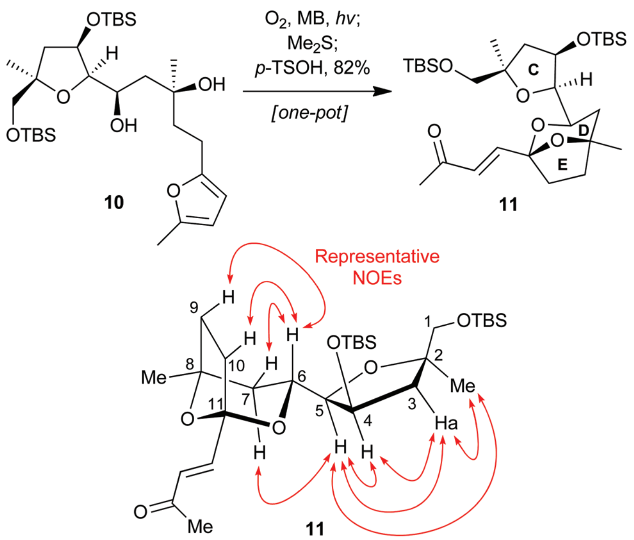
Scheme 2 Synthesis of the C-ring fragment.

the now separable diastereoisomers **5a** and **5b** (**5a** : **5b**, 1 : 1) in 88% overall yield. The relative stereochemistry of the two cyclised compounds was deconvoluted using NOE studies of selected derivatives. More specifically, both diastereoisomers were advanced separately by, firstly, undertaking a double protection of alcohol residues as TBS ethers (yield from **5a** 93%, and from **5b**, 46%), then by DIBALH-mediated reduction of the ester to the primary alcohol (yielding either **6a** or **6b**, in yields of 82 and 89%, respectively). The reason for the low yield obtained for the double protection of **5b** is not immediately clear, but was anyway of little consequence because **6b** was needed only for NOE studies and not for progression of the synthesis. With a key area within the ^1H NMR simplified and extra helpful protons also now introduced, extensive NOE studies were undertaken on both these compounds (**6a** and **6b**) revealing that the relative stereochemistry was that which is shown in Scheme 2. In addition, the primary alcohol of the desired diastereoisomer **5a** was selectively protected as the TBS ether using standard conditions (yield 63%), the remaining secondary alcohol was then converted into each of the two MPA esters separately and the resulting NMR spectra analysed. This confirmed that the expected absolute stereochemistry had been obtained from the Sharpless asymmetric dihydroxylation (for full details, see: ESI†).

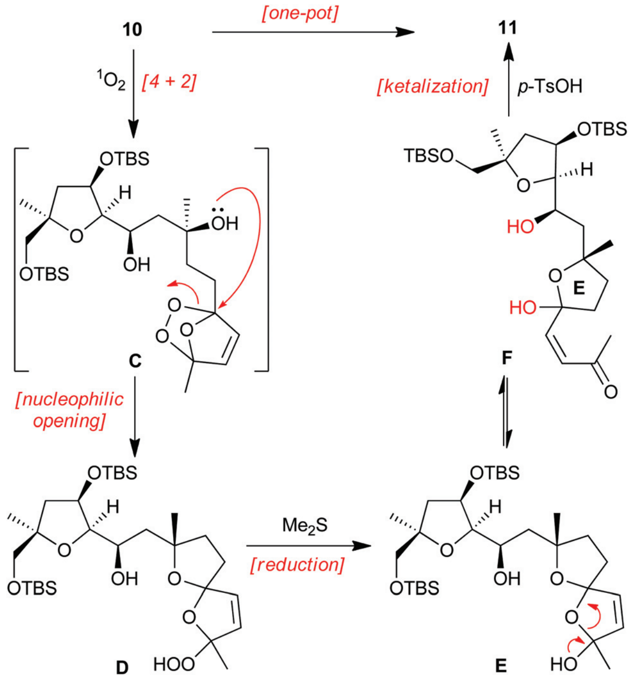
With our C-ring stereochemistry now fully analysed, the synthesis was advanced by oxidation of the primary alcohol of **6a**



Scheme 3 Synthesis of photooxidation substrate **10**.



Scheme 4 Key photooxidation cascade reaction.



Scheme 5 Proposed mechanistic rationale.

using IBX (98%, Scheme 3). The resultant aldehyde **7** was then used as the electrophile in an aldol reaction with the kinetic enolate of furanyl butanone **8**. This aldol reaction proceeded in 70% yield and afforded the desired isomer as the major product (dr 10 : 1).[16] The conditions recently developed by Pihko and co-workers[9a] were then employed to effect the last remaining transformation prior to the key cascade reaction sequence, namely, a stereoselective methylation reaction. The reaction yielded photooxidation substrate **10**, as the major diastereoisomer, in a yield of 65% (the minor diastereoisomer accounted for a further 17%).[16]

The stage was now set for implementation of the crucial cascade reaction sequence (Scheme 4). Thus, photooxidation substrate **10** was subjected to a set of singlet oxygen reaction conditions that have been honed in our laboratory. These include bubbling oxygen gently through the reaction solution containing small quantities (10^{-4} M) of a photosensitiser, in this case, methylene blue, whilst irradiating the cooled solution (ice bath) with a Variac Eimac Cermax 300 W lamp. Following the completion of the initial oxidation steps, as monitored by tlc, an excess of dimethyl sulfide was introduced into the reaction vessel to effect the reduction of the newly formed peroxy residue. Finally, and, once again when tlc monitoring indicated the reduction was complete, trace acid (*p*-TsOH) was added to complete the cascade reaction sequence (Scheme 4). Gratifyingly, each of these stages proceeded exceptionally smoothly and the final product, the completed pectenotoxin CDE-ring unit **11**, was cleanly formed in an extraordinary yield of 82%, as a single stereoisomer. Extensive NOE experiments, as shown in Scheme 4, confirmed the stereochemistry of the final cyclised compound **11**. As expected, a set of NOEs similar to those observed for **6a** were shown for the C-ring of **11**. More importantly, the existence of NOEs between H_6 and both H_9 and H_{10} proves the stereochemistry of the DE-bicyclic ketal in the final compound **11**. In addition, this remarkable cascade reaction sequence could also be adapted so that it could be conducted in water (in this case, using rose bengal as sensitiser), albeit with a slightly reduced yield of 74%, adding to its already excellent green credentials.

The mechanistic rationale for this highly complex cascade reaction sequence is given in Scheme 5. Thus, initial [4 + 2]-cycloaddition of singlet oxygen to the furan fleetingly yields ozonide **C**, which is rapidly opened by the pendant internal nucleophile (a hydroxyl group) to afford the [5,5]-spirocyclic hydroperoxide **D**.[4,6,15,17] All the characteristic peaks corresponding to intermediate **D** were observed in crude ^{1}H NMR spectra of the photooxidation mixture, prior to the addition of dimethyl sulfide. Reduction of the hydroperoxy residue of **D** to hemiketal **E** is followed by acid catalysed rearrangement of the spirocycle and *cis–trans* isomerisation of the double bond, to give the final product **11** *via* intermediate **F**.

To summarise, an ambitious singlet oxygen-mediated cascade reaction sequence has been successfully implemented in a "real" system example, giving us rapid access (only 10 steps) to the complex and complete CDE-ring fragment of the pectenotoxins. The cascade reaction sequence itself showcases a remarkable increase in molecular complexity through an easily implemented laboratory protocol and uses a green and highly selective oxidant, thereby making it a powerful solution to the intransigent problem of how to significantly improve our efficiency when we seek to synthesise complex polyoxygenated polycyclic molecules.

Acknowledgements

The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007–2013)/ERC Grant Agreement No. 277588. We also thank Prof. Robert Stockman and Mr George Procopiou for their help in taking HRMS.

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